

## CLAIMS

We claim:

1. A method of treating thrombosis in a mammal comprising administering to the  
5 mammal a pharmaceutical composition that inhibits thrombosis in the mammal,  
wherein the pharmaceutical composition contains a therapeutically-effective amount  
of a small organic compound that is potent and selective for inhibiting Factor XIa so  
that the differential rate of percent inhibition of thrombosis in the mammal is greater  
than the differential rate of percent increase in bleeding time.
- 10 2. The method of claim 1, in which the differential rate of percent inhibition of  
thrombosis weight in the mammal is at least 50% while the differential rate of percent  
increase in bleeding time is not increased or just measurably increased by less than  
30%.
- 15 3. The method of claim 1, in which the small organic compound has an  $IC_{50}$  for  
inhibiting Factor XIa of less than 10 nM.
4. The method of claim 1, in which the small organic compound has an  $IC_{50}$  for  
20 inhibiting Factor XIa of less than 6 nM.
5. The method of claim 1, in which the small organic compound has an  $IC_{50}$  for  
inhibiting Factor XIa of less than 3 nM.
- 25 6. The method of claim 1, in which the small organic compound is highly selective  
for inhibiting Factor XIa.
7. A method of treating thrombosis in a mammal comprising administration of a  
small organic compound to the mammal having sufficient selectivity and potency for  
30 inhibition of Factor XIa, wherein the administration of the small molecule inhibits  
thrombosis in the mammal with no substantial effect on bleeding times in the  
mammal.

8. The method of claim 7, in which the small organic compound has an  $IC_{50}$  for inhibiting Factor XIa of less than 6 nM.

5 9. The method of claim 7, in which the small organic compound has an  $IC_{50}$  for inhibiting Factor XIa of less than 3 nM.

10 10. The method of claim 7, in which the small organic compound is highly selective for inhibiting Factor XIa.

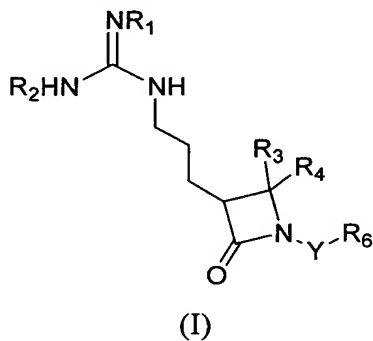
11. A method of inhibiting Factor XIa in a mammal by administration of a small organic compound with an  $IC_{50}$  for inhibiting Factor XIa of less than 120 nM.

12. The method of claim 11, wherein the small organic compound has an  $IC_{50}$  for inhibiting Factor XIa of less than 10 nM.

13. The method of claim 11, wherein the small organic compound has an  $IC_{50}$  for inhibiting Factor XIa of less than 6 nM.

14. The method of claim 11, wherein the small organic compound has an  $IC_{50}$  for inhibiting Factor XIa of less than 1 nM.

15. A method of inhibiting Factor XIa in a mammal by administration of a small organic compound having the formula (I):



wherein:

R<sub>1</sub> and R<sub>2</sub> are hydrogen;

R<sub>3</sub> is hydrogen or CH<sub>3</sub>;

R<sub>4</sub> is selected from hydrogen, CH<sub>3</sub>, -CO<sub>2</sub>R<sub>7</sub>, -C(=O)NR<sub>8</sub>R<sub>9</sub>, phenyl, benzyl, and phenylethyl, wherein R<sub>7</sub> is hydrogen, C<sub>1-6</sub>alkyl, benzyl, or -CH(OCOCH<sub>3</sub>)CH<sub>3</sub>;

5 and each R<sub>4</sub> group is optionally substituted with one to two R<sub>12</sub>;

Y is C(=O) or -SO<sub>2</sub>-; wherein when Y is C(=O), then R<sub>6</sub> is C<sub>1-6</sub>alkyl, aryl, heteroaryl, or -NR<sub>10</sub>R<sub>11</sub>, and when Y is -SO<sub>2</sub>-, then R<sub>6</sub> is aryl or heteroaryl; and each R<sub>6</sub> group is optionally substituted with one to two R<sub>12</sub>;

10 R<sub>8</sub> and R<sub>9</sub> are individually selected from hydrogen and C<sub>1-6</sub>alkyl, or R<sub>8</sub> and R<sub>9</sub> taken together form a five or six membered heterocyclo ring optionally substituted with one to two R<sub>12</sub> and up to one R<sub>13</sub>;

R<sub>10</sub> and R<sub>11</sub> are individually selected from hydrogen, phenyl, or C<sub>1-6</sub>alkyl optionally substituted with phenyl, or R<sub>10</sub> and R<sub>11</sub> taken together form a five or six membered heterocyclo ring optionally substituted with one to two R<sub>12</sub> and up to one  
15 R<sub>13</sub>;

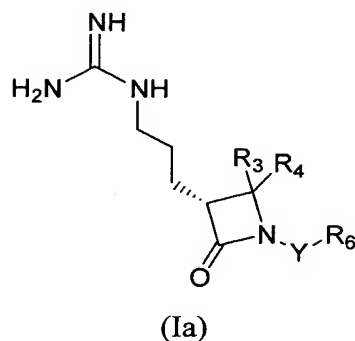
R<sub>12</sub> is selected from hydrogen, halogen, trifluoromethyl, trifluoromethoxy, lower alkyl, amino, lower alkylamino, -CO<sub>2</sub>H, -CO<sub>2</sub>(lower alkyl), or a five or six membered saturated or unsaturated heterocyclo having up to two nitrogen heteroatoms;

20 R<sub>13</sub> is selected from -C(=O)(C<sub>1-6</sub>alkyl), -CO<sub>2</sub>(C<sub>1-6</sub>alkyl), -C(=O)NH(C<sub>1-6</sub>alkyl), and five or six membered heterocyclo optionally substituted with one to two R<sub>14</sub>; and

R<sub>14</sub> is selected from hydrogen, phenyl, or C<sub>1-6</sub>alkyl optionally substituted with phenyl;

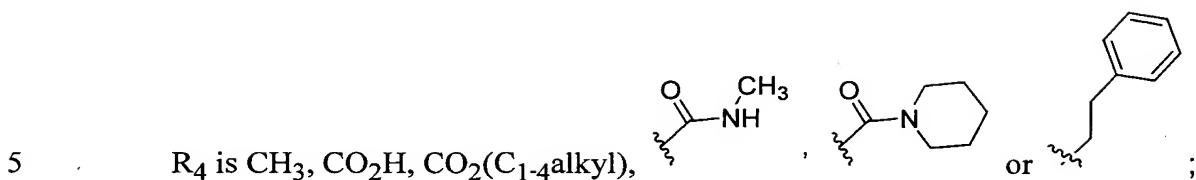
25 or a prodrug carbamate thereof wherein at least one of R<sub>1</sub> and R<sub>2</sub> is COOR, wherein R is hydrogen, C<sub>1-6</sub>alkyl, benzyl, or CH(OCOCH<sub>3</sub>)CH<sub>3</sub>, or a pharmaceutically-acceptable salt or hydrate of said compound or prodrug carbamate.

16. The method of claim 15, wherein the small organic compound has the formula  
30 (Ia):



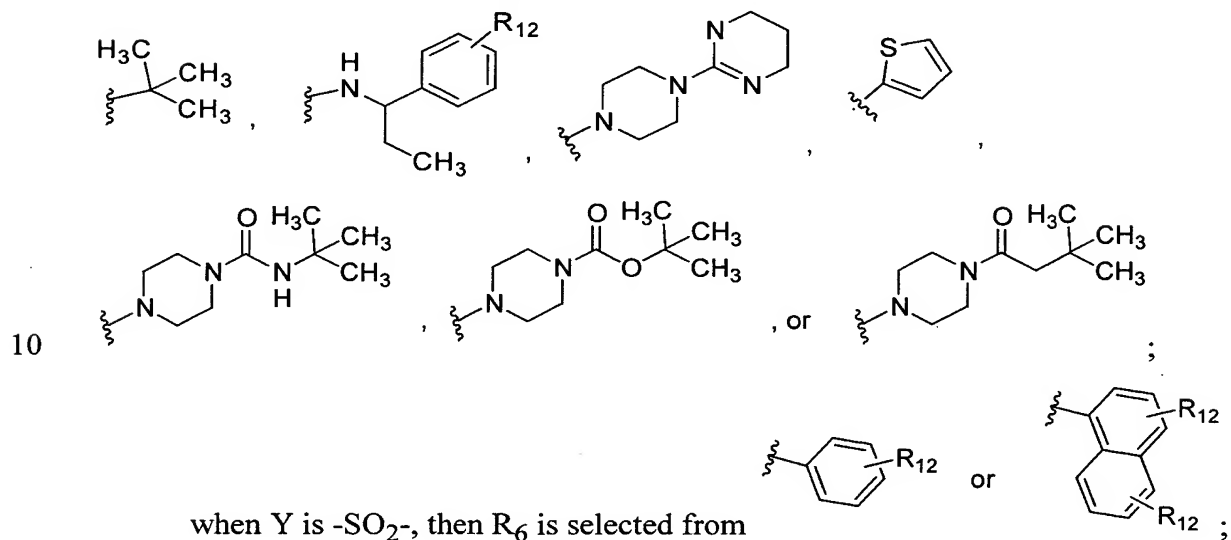
wherein:

$R_3$  is hydrogen or  $\text{CH}_3$ ;



$Y$  is  $\text{C}(=\text{O})$  or  $-\text{SO}_2-$ ; wherein:

when  $Y$  is  $\text{C}(=\text{O})$ , then  $R_6$  is methyl, ethyl propyl,

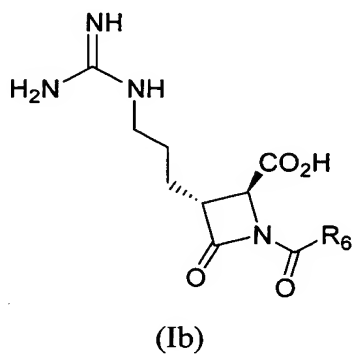


and

$R_{12}$  is selected from hydrogen, lower alkyl, amino, lower alkylamino,  $-\text{CO}_2\text{H}$ ,  
 and  $-\text{CO}_2(\text{lower alkyl})$ ; or a prodrug carbamate thereof wherein at least one of  $R_1$   
 15 and  $R_2$  is  $-\text{COOR}$ , wherein  $R$  is hydrogen,  $\text{C}_{1-6}\text{alkyl}$ , benzyl, or  $-\text{CH}(\text{OCOCH}_3)\text{CH}_3$ ,  
 or a pharmaceutically-acceptable salt or hydrate of said compound or prodrug

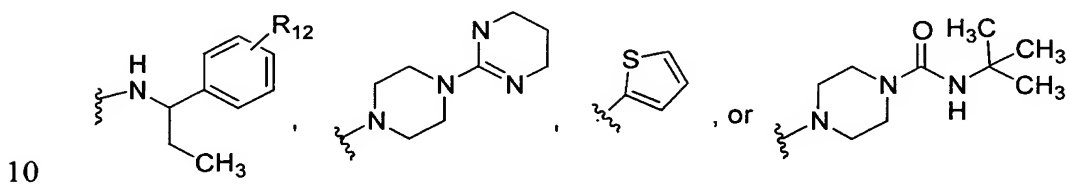
carbamate; wherein the compound has an IC<sub>50</sub> for inhibiting Factor XIa of less than 20 nM.

17. The method of claim 15, wherein the small organic compound has the formula  
5 (Ib),



wherein:

$R_6$  is selected from:



or a prodrug carbamate thereof wherein at least one of R<sub>1</sub> and R<sub>2</sub> is -COOR, wherein R<sub>12</sub> is defined as above; R is hydrogen, C<sub>1-6</sub>alkyl, benzyl, or -CH(OCOCH<sub>3</sub>)CH<sub>3</sub>, or a pharmaceutically-acceptable salt or hydrate of said compound or prodrug carbamate; wherein the compound has an IC<sub>50</sub> for inhibiting Factor XIa of less than 3 nM.